TSR/DHY/WH

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
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FEB 12 2004
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PCT

WRITTEN OPINION

(PCT Rule 66)

Applicant's or agent's file reference 033388-531	Date of Mailing (*day/month/year*) 11 FEB 2004 REPLY DUE within 1 months/days from the above date of mailing

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US03/00380	08 January 2003 (08.01.2003)	09 January 2002 (09.01.2002)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 9/27; C12N 15/88; A01N 43/04 and US Cl.: 424/450; 514/4; 435/458

Applicant

ELAN PHARMACEUTICALS,INC.

1. This written opinion is the first (first, etc,) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 09 May 2004 (09.05.2004).

Name and mailing address of the IPEA/US
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Form PCT/IPEA/408 (cover sheet)(July 1998)

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GPS 2-18-04

Response to Written Opinion due 3/11/04

FEB 13 '04
2-13

WRITTEN OPINION

International application No.
PCT/US03/00380

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:
pages 1-38, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 39-69, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-9, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."*

WRITTEN OPINION

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 143, 145

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 143, 145 are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. 143,145.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Inventive Step (IS)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Industrial Applicability (IA)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-34 and 38-73, 147, 149, 153-167 lack novelty under PCT Article 33(2) as being anticipated by Eppstein et al (US Patent 4897335).

Claims 1-34 and 38-73 are directed to liposomes comprising nucleic acids. The liposomes are made by a particular process which has been given no patentable weight in the determination as to whether the claimed products are novel. Eppstein teaches a variety of liposomes comprising nucleic acids. The liposomes may comprise varying amounts of the fusogenic lipid DOPE. The nucleic acid may be plasmid DNA, or an antisense RNA oligonucleotide. The liposomes may comprise a variety of lipids including distearoyl phosphatidylcholine and cholesterol. Eppstein also teaches intravenous delivery to humans. See entire document.

Claims 1-6, 8-17, 25, 29-31, 33, 34, 38-79, 87, 90-104, 142, 144, and 153-167 lack novelty under PCT Article 33(2) as being anticipated by Papahadjopolous et al (US Patent 4235871).
Claims 1-6, 8-17, 25, 29-31, 33, 34 are directed to liposomes comprising nucleic acids. The liposomes are made by a particular process which has been given no patentable weight in the determination as to whether the claimed products are novel.
Papahadjopolous teaches a variety of liposomes comprising nucleic acids. The liposomes may comprise varying amounts of the fusogenic lipid DOPE. The nucleic acid may be plasmid DNA, or an RNA. The liposomes may comprise a variety of lipids including distearoyl phosphatidylcholine and cholesterol. See entire document.
Papahadjopolous teaches a method of making liposomes by combining lipids and nucleic acids in an organic solvent to form an emulsion, and thereafter forming a gel in which are subsequently formed liposomes. See entire document, especially e.g. claim 1.

Claims 7, 18-24, 26-28, 32, 80-86, 88, 89, 105-107, 111-141, 146-148, 150, 151, 152, and 168 lack an inventive step under PCT Article 33(3) as being obvious over Papahadjopolous et al (US Patent 4235871), in view of Eppstein et al (US Patent 4897335).
The teachings of Papahadjopolous are described above. Presently claimed limitations concerning the amount of lipids in gels or liposomes, the identity of organic solvents used in liposome formation, the order in which components are added to mixtures, the size of plasmid DNAs, and the identity of liposome forming lipids are taken to be parameters that are routinely optimized by those of ordinary skill in the art, particularly in view of the teachings of Eppstein who discloses a variety of lipids, solvents, and nucleic acids. Eppstein also teaches the use of these liposomes to deliver bioactive substances such as nucleic acids in vivo by intravenous administration. See entire document.

Claims 35-37 and 108-110 lack an inventive step under PCT Article 33(3) as being obvious over Papahadjopolous et al (US Patent 4235871) in view of Meers et al (US Patent 6,120,797).
The teachings of Papahadjopolous are described above. Papahadjopolous does not teach N-acyl phosphatidylethanolamines.
Meers teaches a N-dodecanoyl dioleoyl phosphatidylethanolamine for use in liposome formation.
It would have been obvious to use the lipid of Meers in the liposomes of Paphadjopolous because Meers teaches that it promotes membrane fusion. See e.g. column 1, lines 48-60.

---------- NEW CITATIONS ----------

WRITTEN OPINION

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:
The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

V.1. Reasoned Statements:
The opinion as to Novelty was positive (Yes)with respect to claims 35-37, 80-86, 88, 89, 105-142, 145, 146, 148, 150-152, and 168
The opinion as to Novelty was negative (No) with respect to claims 1-34, 38-79, 87, 90-104, 142, 144, 147, 149, 153-167
The opinion as to Inventive Step was positive (Yes)with respect to claims NONE
The opinion as to Inventive Step was negative(NO) with respect to claims 1-142, 144, 146-168
The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-142, 144, 146-168
The opinion as to Industrial Applicability was negative(NO) with respect to claims NONE